

Early diffusion changes following controlled cortical impact injury on a rat model

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Introduction:

The understanding of tissue alterations at an early stage following traumatic brain injury (TBI) is critical for injury management and prevention of more severe secondary damage. Previous studies have shown decreased apparent water diffusion (ADC) within hours after TBI followed by increased diffusion, days or weeks after TBI^{1,2}. Understanding tissue changes very early following injury can provide an insight into possible treatment windows. In this study, we investigated the early changes in tissue water diffusion following mild to moderate controlled cortical impact injury using a rat model.

Methods:

TBI model: Six adult male Sprague-Dawley rats (300-350 gms) were subjected to left parietal controlled cortical impact injury [1]. After being anesthetized initially with 4% isoflurane, the rats were maintained at 2% isoflurane, and the left parietal bone was exposed via a midline incision in a stereotactic frame. A high-speed dental drill was used to perform a left-sided 5 mm craniotomy that was centered 3.5 mm posterior and 4 mm lateral to bregma. A 5 mm round impactor tip was accelerated to 5 m/sec with a vertical deformation depth of 1.0-1.5 mm and impact duration of 50 ms. The bone flap was immediately replaced with dental acrylic and the scalp incision was closed with 3.0 silk. The experimental protocol was approved by the Committee for the Welfare of Laboratory Animals of the University of Maryland.

Imaging: All imaging was performed on a Bruker Biospec 7.0 Tesla 30 cm horizontal bore scanner using Paravision V software. A Bruker surface array coil was used as the receiver and a Bruker 72mm linear-volume coil as the transmitter. T₂-weighted (TE/TR = 56.8/5500ms, 4 echo train length, 2 averages) and diffusion weighted images (TE/TR = 50/6000ms, single shot spin echo EPI, 30 directions, 5 b₀ images, b = 1000s/mm², 2 averages) were acquired at before the injury and 2 hour and 4 hour after injury. During the entire imaging time, the animal was under 1-2% isoflurane anesthesia and 1 L/min oxygen administration via a nosecone. Both respiration and heart rate were monitored.

DTI Analysis: DTI maps were generated offline using FDT (FMRIB's Diffusion Toolbox, Oxford, UK). Regional measures of ADC and FA were obtained from the hippocampus, thalamus and the olfactory regions of both the ipsilateral and contralateral side of the injury site as shown in Figure 1. Changes in DTI parameters were compared with the control time point using two sample paired t-test.

Results:

Figure 1 shows T₂-weighted axial and coronal slices, FA and ADC maps of a representative rat after injury. Figure 2 shows average ADC and FA values from the six ROI's shown in Figure 1 at 2 hour and 4 hour after injury. At 2 hour after injury, ADC was significantly reduced and FA increased (p<0.05) in the ipsilateral hippocampus. FA was also increased (p<0.05) in the ipsilateral thalamus. Although non-significant, a trend for ADC reduction was observed bilaterally in the thalamus and the ipsilateral olfactory region (p<0.1). For FA, an increasing trend (p<0.1) was also observed for the contralateral hippocampus while a decreasing trend (p<0.1) was observed in the olfactory region. At 4 hour after injury, a significant increase in FA (p<0.05) was observed in the ipsilateral hippocampus and the thalamus. An increasing trend (p<0.1) for FA was observed in the contralateral hippocampus and thalamus. Although changes in DTI metrics remained abnormal from the baseline both in the hippocampus and the thalamus at the 4 hour point, this outcome was quite variable due to the inter-individual differences compared to the 2 hr time point.

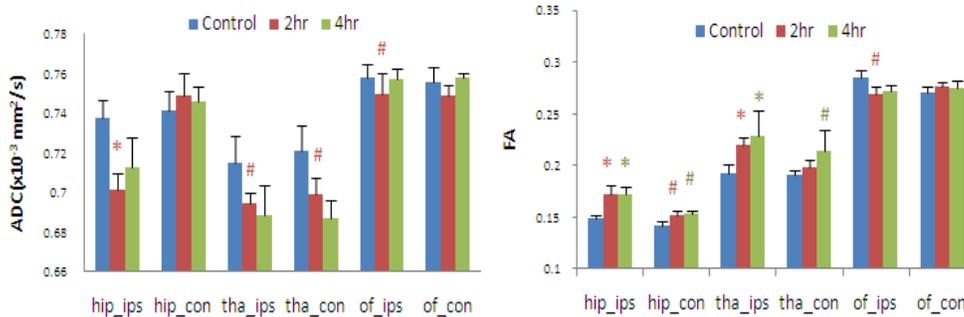


Figure 2. Regional ADC and FA values at 2 hour and 4 hour after TBI for hippocampus ipsilateral (hip_ips) and contralateral (hip_con), thalamus ipsilateral (tha_ips) and contralateral (tha_con), olfactory ipsilateral (of_ips) and contralateral (of_con). Error bar shows standard error (= standard deviation/√sample size). (* is for significance level of p < 0.05. # is for significance level of p < 0.1.)

Discussion:

This study showed a decreased ADC and increased FA in regions in close proximity to impacted regions (ipsilateral hippocampus and bi-lateral thalamus) immediately following TBI, with the ipsilateral hippocampus most affected, followed by ipsilateral thalamus and contralateral thalamus. Remote regions such as the ipsilateral olfactory area were affected to a lesser degree. At the 4 hour time point a large inter-individual variation was observed with an overall trend towards recovery in the ipsilateral hippocampus while the thalamus was still going through significant worsening stage. Our study indicates a distance effect from the site of injury and suggests a therapeutic window of about 2-3 hours to limit the cascade of events that may lead to secondary injury.

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Reference:

[1] Albenis BC, et al., Exp. Neurol. 162, 61–72. [2] Obenaus A, et al., J. Neurotrauma 24, 1147–1160.